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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/825,867	04/16/2004	Jason W. Chin	54-000240US	8312

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EXAMINER
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GEBREYESUS, KAGNEW H

ART UNIT	PAPER NUMBER
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1656

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05/09/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

10/825,867

Applicant(s)

CHIN ET AL.

Examiner

Kagnew H. Gebreyesus

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 26 March 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-138 is/are pending in the application.
- 4a) Of the above claim(s) 1-37, 58-130 and 134-138 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 38-57 and 131-133 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>11/8/04</u> . | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

Applicant's election without traverse of Group III comprising claims 38-57 and 131-133 in the reply filed on February 01, 2007 is acknowledged. Claims 1-37, 58-130, 134-138 are withdrawn from further consideration as being part of non-elected subject matter. Claims 38-57 and 131-133 are present for examination.

### ***Priority***

Acknowledgment is made to this Application which claims priority from provisional applications USSN 60/463,869 filed April 17, 2003; USSN 60/479,931 filed June 18, 2003; USSN 60/493,014 filed August 5, 2003 and USSN 60/496,548 filed August 19, 2003.

### ***Information Disclosure Statement***

The information disclosure statement filed on November 08, 2004 for which a copy of the patent publication has been submitted in this application has been considered as shown by the Examiners signature next to each reference.

### ***Oath/Declaration***

The oath or declaration submitted on April 16, 2004 has been reviewed and is in compliance with 37 CFR 1.56.

### ***Specification***

The disclosure is objected to because it contains an embedded hyperlink and/or

other form of browser-executable code in paragraphs [0184] and [0294]. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See M.P.E.P. § 707.05(e) for the acceptable notation of an internet address.

Furthermore the specification is objected to for an unclear incorporation by reference. In paragraphs [0177] and [0181], reference to a related case by attorney docket number is unclear. The Examiner suggests use of either the Patent Application Publication number of the other application (preferable) or the application number for clarity. Correction is required.

In addition the specification comprises redundancy in various sections. For example paragraph [0196] is substantially a duplicate of paragraph [0061]; paragraph [0097] substantially duplicates paragraph [0062]; paragraph [0198] duplicates paragraph [0063]; paragraph [0356] substantially duplicates paragraph [0191] etc. In the interest of clarity and timely examination, it is suggested that Applicants avoid reiterating subject matter previously covered.

### ***Claim Objections***

Claims 38-57 and 131-133. are objected to for the recitation "at least one unnatural amino acid" and the term "at least one post-translational modification." The metes and bounds of this term in both occurrences are unclear. Can all of the residues in said protein be unnatural and still retain it's functional property? (e.g. Gal4 protein wherein all the amino acids are unnatural) Clarification is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 48 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 48 and 49 are rejected for the recitation "at least 75% identical to that of a therapeutic protein, a diagnostic protein..." Without a disclosure of any structure it is unclear how a skilled artisan can conceive a protein that is at least 75% identical to a hypothetical protein. Clarification is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-57, 131-133 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a protein with a limited number of unnatural amino acids selected from para-acetyl-L-phenylalanine or para-iodo-L-phenylalanine or O-methyl-L-tyrosine or para-propargyloxy-phenylalanine or para-azido-phenylalanine, does not reasonably provide enablement for a protein comprising any number (up to 100%) and/or variety of unnatural amino acids.

The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)). The *Wands* factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim. While the above factors are considered, a sufficient amount of *prima facie* case is discussed below..

Claim 38 is so broad as to encompass any protein that comprises any number of unnatural amino acids. Furthermore claims 39-49, 53-57, 131-133 are so broad as to encompass any protein that comprises any number of unnatural amino acids which can further be post-translationally modified with at least one saccharide moiety or wherein the post-translationally modification comprises acetylation, acylation, lipid modification, palmitoylation, palmitate addition, phosphorylation and glycolipid-linkage modification.

The specification in Paragraph [0347] teaches how to make human superoxide dismutase 1 (hSOD) comprising each of the unnatural amino acid para-acetyl-L-phenylalanine or para-iodo-L-phenylalanine or O-methyl-L-tyrosine or para-propargyloxy-phenylalanine or para-azido-phenylalanine. The specification does not teach how to make or use any protein that comprises any number of unnatural amino acids which can further be post-translationally modified by any saccharide moiety or

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wherein the post-translationally modification comprises acetylation, acylation, lipid modification, palmitoylation, palmitate addition, phosphorylation and glycolipid-linkage modification.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of possible polypeptides broadly encompassed by the claims. The function of a protein comprising any number of and/or any variety of unnatural amino acid(s) would be unpredictable for the following reasons.

The specification in paragraph [0040], [0048] and specifically on page 15, line 1-5 teaches a method for incorporating unnatural amino acids wherein a protein of interest is made using a nucleic acid comprising at least one, two...ten or more selector codons. However the specification does not teach how such a protein can be made by any example. Even if "*pro-arguendo*" it was possible to make such a protein, this would require modifying all or nearly all of the coding sequences of a nucleic acid to selector codons which would then produce a mosaic of proteins comprising an unspecified number of unnatural amino acids (because of the limited number of selector codons) thus the function of such a protein would be unpredictable.

Furthermore the specification in paragraph [0047] teaches that selector codons include stop codons (e.g., an amber-codon, an ochre codon, or an opal stop codon), nonsense codons, rare codons, four (or more) base codons, and/or the like. However, the specification does not provide adequate guidance on how these limited number of selector codon combinations would suffice to produce a polypeptide comprising up to

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100% of unnatural amino acids further comprising unlimited number of post-translational modifications i.e. Applicants have not provided any direction or guidance or have provided a working example for any protein(s) comprising up to 10%, 20%, 30%... 100% unnatural amino acids which can further comprise any number of post-translational modifications and retain a desired structure/function. Therefore the breadth of the claims encompasses a scope not enabled by the specification. The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific unnatural amino acid(s) incorporated and the specific post-translational modification(s). Without such guidance, the experimentation left to those skilled in the art is undue.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351.

Claims 39-42, 45-57 and 131-133 are rejected under 35 U.S.C. 102(e) as being anticipated by Schultz et al (US 7,129,333 B2) which claims priority from U.S. provisional patent application Ser. No. 60/419,265, filed Oct. 16, 2002.

The applied reference has a common inventor with the instant application.



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Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Schultz et al disclose compositions comprising a protein (glycoprotein) wherein at least one unnatural amino acid such as para-acetyl-L-phenylalanine (a keto amino acid) (see example #3, Schultz et al) is incorporated and further modified with saccharide moieties (as applied to claims 39, 40, 41 and 42). Claim 41 and 42 are included in this rejection because these claims are directed to products. The embodiments in claims 45, 47 and 133 wherein the post-translational modification comprises an unnatural amino acid with a saccharide moiety including a serine or threonine amino acid, such as, Glc-L-threonine, GlcNAc-L-serine, alpha.-GalNAc-L-threonine, O-GalNAc-L-serine are anticipated by the disclosure of Schultz et al page 33 line 7-26. Schultz et al also teach enzymatic coupling a Galactose with GlcNAc in example 3 (page 57, 14-25) thus producing GalGlcNAc thus anticipating claim 46. Furthermore Schultz et al describe other posttranslational modifications comprising acetylation and phosphorylation in paragraph example 4 (page 60 line 44-46). Composition of glycoproteins that have 75% (60%-99%) identity to that of a therapeutic protein are disclosed by Schultz et al in page 16 line 1-6. Furthermore page 15 line 34-36 of Schultz et al teaches that the glycoprotein composition can comprise 1-10 unnatural amino acids that can be the same or different. A composition comprising 100 micrograms or 50 microgram/L of a

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glycoprotein in a pharmaceutical buffer is taught in page 14 lines 52-53 of Schultz et al. Schultz et al also teach use of an epitope tag on the protein comprising the unnatural amino acid on page 27 lines 1-8 of their disclosure.

Claims 38 and 131 are rejected under 35 U.S.C. 102(b) as being anticipated by Kiga et al (An Engineered Escherichia coli tyrosyl-tRNA synthetase for incorporation of an unnatural amino acid into proteins in eukaryotic translation and its application in wheat germ cell-free system. Proceedings of the National Academy of Sciences 2002 Jul. 23;99(15): 9715-9723). Kiga et al teach the incorporation of the unnatural amino acid 3-iodo-L-tyrosine into a protein (human c-Ha-Ras) in a eukaryotic translation system. Figure 2, lane three of Kiga et al shows the production of human c-Ha-Ras comprising the unnatural amino acid, 3-iodo-L-tyrosine. Claim 131 is drawn to a protein comprising any unnatural amino acid wherein said protein is produced in a eukaryotic cell. Thus Kiga et al's protein comprising 3-iodo-L-tyrosine produced in a eukaryotic system anticipates claim 131. Claim 38 is anticipated because it recites: A composition comprising a Gal4 protein or a portion thereof..." which, encompasses any protein comprising even a single amino acid from the Gal 4 protein. Therefore the teaching of Kiga et al anticipates claim 38.

Claims 38 and 131 rejected under 35 U.S.C. 102(a) as being anticipated by Sakamoto et al (Site-specific incorporation of an unnatural amino acid into proteins in mammalian cells Nucleic acid Research, 2002, Vol. 30 No. 21). Sakamoto et al disclose

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use an orthogonal tRNA/OtRNA synthetase pair derived from *Bacillus* tRNA<sup>Tyr</sup> and *E. coli* tRNA<sup>Tyr</sup> synthetase to produce a protein (human c-Ha-Ras) comprising 3-iodo-L-tyrosine in eukaryotic cells (CHO-Y cells). As stated above claim 38 is rejected because it recites: "A composition comprising a Gal4 protein or a portion thereof..." which, encompasses any protein comprising even a single amino acid from the Gal 4 protein. Claim 131 is rejected because Sakamoto et al teach the production of a protein comprising 3-iodo-L-tyrosine produced in a eukaryotic cell.

Claims 131 and 132 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al. *Journal of American Chemical Society* 2001. Vol. 123 (37) p 8883-8886). Wang et al. teach phosphorylation of unnatural tyrosine analogues comprised in the Src protein. On page 8884, Wang et al teach semi-synthetic proteins wherein a tyrosine residue at position 527 was replaced with said unnatural amino acid and wherein said semi-synthetic proteins were used as Csk (a protein tyrosine kinase that phosphorylates Src) substrates. Fig. 4 shows a commassie stained 10% SDS-PAGE for a Src protein comprising a  $\beta$ -methyl tyrosine (lane 2), or an amino-phenylalanine (lane 3) were said unnatural analogues were further phosphorylated. Thus claims 131-133 drawn to proteins comprising an unnatural amino acid with further modification is anticipated by Wang et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagnaw H. Gebreyesus whose telephone number is 571-272-2937. The examiner can normally be reached on 8:30am-5:30pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kagnew Gebreyesus PhD.  
Art Unit 1656  
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March 30, 2007

  
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SUPERVISORY PATENT EXAMINER